CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number: NDA 20-587

APPROVAL LETTER

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-587

DEC 24 1997

Bryan Corporation
4 Plympton Street
Woburn, MA 01801

Attention: Frank Abrano
Chief Executive Officer

Dear Mr. Abrano:

Please refer to your new drug application dated August 11, 1995, and to your resubmission dated November 13, 1997, received November 17, 1997, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sclerosol Intrapleural Aerosol (sterile talc powder).

We acknowledge receipt of your amendment dated December 5, 1997.

The User Fee goal date for this application is May 16, 1998.

This new drug application provides for the prevention of the recurrence of malignant pleural effusions in symptomatic patients.

We have completed the review of this application, including the submitted draft labeling, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the draft labeling in the submission dated November 13, 1997. Accordingly, the application is approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the draft labeling submitted on November 13, 1997. Marketing the product with FPL that is not identical to this draft labeling may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FINAL PRINTED LABELING" for approved NDA 20-587. Approval of this submission by FDA is not required before the labeling is used.

Should additional information relating to the safety and effectiveness of the drug become available, revision of that labeling may be required.

We remind you of your agreement, in your facsimile of December 24, 1997, to provide the following information:

1. An appropriate expiration time for the drug product.

2. Use of sampling time points under the stability protocol, as described in the Guidance for Stability Testing of Drug Products of: 0, 3, 6, 9, 12, 18, and 24, months. Time points may not be omitted until generation of a significant amount of stability data.

3. The results of release testing on the demonstration batches manufactured by Sciarra Laboratories. Additional data from the supplies that were shipped under emergency INDs may supplement these results.

4. With regard to the regulatory specifications and methods for the drug product, a detailed description of the procedures for the coulemetric water determination per USP <921> Method Ic, including the transfer of the sample between the pressurized aerosol container and the Karl Fischer apparatus.

5. Based on the specifications, which indicate that the specification for the minimum percent passing through the mesh screen should be set at a higher value, a new limit with supporting data as justification.

6. Stress testing to include low temperature cycling and at elevated temperature and humidity of the finished product. (Please note these tests need to be performed only once.)

7. With regard to the valve function test, in-process testing should be performed on one canister every thirty minutes selected randomly. Release testing will involve sampling 1%, or not less than 40 canisters, of each production lot. In addition, 100 canisters will also be tested for valve function during sterility testing. If any failures are detected, you must consult the Division for evaluation and disposition.

8. The identity of the testing laboratory that will test for the absence of asbestos in the bulk talc material. We understand that is no longer in business.

In addition, we note the following:

1. The particle size distribution specification of "NMT particles greater than microns in diameter" should include agglomerates unless sufficient justification can be provided to exclude this morphology.

2. SOP S-0023-01 (Microbiological testing of environmental conditions in the warehouse and manufacturing area) does not include incubation parameters for plates. These should be included.

3. There appears to be confusion about the purpose of the endotoxins test. This test is not linked with an assessment of microbial growth in the container (refer to your second sentence in reply to question 5). Because the raw talc is mined from the earth and washed with water to remove top soil, there is sufficient reason for concern about residual polysaccharide toxin from dead microbes in the soil or water. Similarly, we disagree with the argument suggesting the endotoxins requirement is inappropriate due to the product's intrapleural use, i.e., not a product administered by injection into the blood stream. We recommend an endotoxins limit of 350 EU per canister. Please validate your endotoxins testing procedure.

Please submit the above information and any response to our comments to the NDA as correspondence.

In addition, we request under 21 CFR 314.81(b)(2)(vii) that you include in your annual report to this application, a status summary of each commitment.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to the Division of Oncology Drug Products and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please contact Debra Catterson, Project Manager, at (301) 827-1544.

Sincerely yours,

/S/ 12/24/97

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

cc:
Original NDA 20-587
HFD-150/Div. files
HFD-150/CSO/D.Catterson
HFD-150/AMartin
HFD-150/JBeitz
HFD-150/RBarron
HFD-150/RWood
HFD-150/WSchmidt
HFD-150/PAndrews
HFD-150/ARahman
HFD-150/LKieffer
HFD-150/TKoutsoukos
HFD-805/DHussong
HFD-350/NSager
HFD-002/ORM (with labeling)
HFD-101/Office Director
HFD-810/ONDC Division Director
DISTRICT OFFICE
HF-2/Medwatch (with labeling)
HFD-92/DDM-DIAB (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-735/DPE (with labeling) - for all NDAs and supplements for adverse reaction changes.
HFI-20/Press Office (with labeling)
HFD-021/ACS (with labeling)

Drafted by: DCatterson/December 22, 1997/c:\wpfiles\nda's\talc\letter.ap
r/d initialed by:
AChapman/12.23.97
AMartin/12.22.97
JBeitz/12.22.97
RBarron/12.23.97
RWood/12.23.97
WSchmidt/12.22.97
PAndrews/12.22.97
ARahman/12.22.97
LKieffer/12.22.97

F/T by DCatterson/12.24.97
RDeLap/date RD 12/24/97

APPROVAL (AP) [with Phase 4 Commitments]

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20-587

APPROVABLE LETTER

OCT 27 1997

NDA 20-587

Bryan Corporation
4 Plympton Street
Woburn, MA 01801

Attention: Frank Abrano
Chief Executive Officer

Dear Mr. Abrano:

Please refer to your new drug application dated August 11, 1995, and to your resubmission dated April 28, 1997 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sclerosol Intrapleural Aerosol (sterile talc powder).

We acknowledge receipt of your amendment dated August 6, 1997.

The User Fee goal date for this application is October 29, 1997.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Before this application may be approved, however, it will be necessary for you to respond to the following deficiencies:

The following deficiencies pertain to the chemistry portion of your application:

Please provide the following information concerning the talc drug product to the new drug application:

1. During an FDA inspection on August 13-19, 1997 of the Sciarra Laboratories, Inc. facility, significant differences were found between the manufacturing procedures described in the NDA for the drug product and those actually being used in the facility. Please provide a current, complete, and detailed manufacturing production record which gives the step-by-step manufacturing instructions, the drug product components to be used, equipment to be used, in-process tests that are performed, and acceptance tests and analytical methods used for all starting components and for the drug product.

2. Provide representative, current batch records for drug product manufactured according to the Master Production Record given in (1) above, including the batch numbers, the source and test results for all components used, and analytical results for the drug product tested according to the Sciarra Laboratories, Inc. specifications and methods described in (3) below.

3. Provide the regulatory specifications and analytical methods for the drug product manufactured by Sciarra Laboratories (prior to sterilization), including those for satisfactory operation of the valve and actuator, the particle size distribution of the talc aerosol (minimum and maximum size limits as well as size distribution between the minimum and maximum values), the number of sprays obtained per canister, the amount of talc delivered with each spray, and the microbiological burden for one spray and for the entire canister.

4. Provide to the NDA, the acceptance specifications and tests methods used by for the talc drug product prior to sterilization. Provide a detailed, step-by-step copy of the master production record used by for the sterilization of the drug product.

5. Provide information on the acceptance tests and methods used by for the talc drug product received from after sterilization. Provide a copy of the step-by-step procedure used by for sterility testing of the drug product, including full information on the sampling plan and testing procedures which are used.

6. Provide to the NDA, the current regulatory specifications and analytical methods used by Sciarra for the talc drug product sterilized by and sterility tested by The specifications should include those for the integrity and operation of the valve and actuator components, the integrity of the canister and absence of leakage, the fill and purity of the canister contents, and the consistency and suitability of the talc spray, including particle size distribution range (upper and lower ranges and intermediate distribution values).

7. A stability protocol and at least six months of stability data need to be provided for the finished radiation-sterilized talc drug product. The data should cover the full range of used in the sterilization process and, at appropriate intervals, the device should be taken apart and examined for radiation damage, e.g., to the gaskets and other components and to the inner lining of the canister. The drug product should be examined for possible contamination by the canister lining or device degradation products. The particle size distribution of the talc aerosol should also be monitored as well as other stability-indicating parameters.

8. Provide the sampling plans for the selection of representative samples of the sterilized finished drug product for release testing.

Please provide the following information concerning the talc drug substance.

1. Concerning the bulk talc drug substance obtained from , please provide to the NDA the current specifications and analytical methods used by for the talc which is provided to Sciarra Laboratories. Information is also requested on whether the talc must also meet other standards, e.g. those for cosmetics. Provide the current acceptance specifications and test methods used by Sciarra Laboratories forth bulk talc provided by

2. The USP 23 monograph on Talc requires an identification test. A test should be added to the list of specifications and results reported on all certificates of analysis.

3. The specification for the in-process tests for bulk density, sieve analysis and particle size distribution used in the processing of crude talc should be provided.

4. reports the levels of ferric oxide in parts per million while the specification sheet requires % weight. This difference should be eliminated and it is believed the ppm is the correct specification.

5. Whiteness is determined by using a filter, whereas the specification refers to min). This difference should be addressed.

   It should be noted that the current USP certification found in Exhibit B of the inspection specifies for the bulk . The differences between measurement scales should be reconciled.

6. In the summary of findings of the FDA-483, dated 12-SEP-1997 submitted by M. Gronsky, a revised specification sheet for USP Certification is provided. The revision includes the addition of limits at 90% um) and 10% um) of the particle size distribution. The NDA submission should be revised to included these limits in addition to the basis for establishment of the limits.

7. As a minimum, the product contact surface, in this case the composition of the plastic bag, should be more full described. Citation to the regulations for food contact use should be stated. Stability studies should be conducted to reveal any potential long term impact, leachables, the contact surface may have on the bulk material.

8. A specification of % minimum passing through the mesh screen should be revised, since the specifications set the limit of % of the material should be below microns (limits of microns).

The following deficiencies pertain to the microbiology portion of your application:

1. A summary of the validation of the sterilization process for the drug product, Sclerosol, has not been provided. We recommend that a summary be provided in the NDA. Validation summaries should describe the process, the sterilizer, the sterilizer load size(s) and load configuration, validation methods, dose determination, dose ranges and biological measures. Experiment dates and a summary of the data should be included. Acceptance criteria for validation experiments and for production load sterilization should be provided.

2. The manufacturing area at was described as a manufacturing room with a controlled environment (page 970146).

   a. Please provide a drawing of the layout of the area, indicating the flow of product and components, the equipment used to package the product, and the air classification for the processing areas.

   b. The last paragraph of that page states that low particulate count is maintained and monitoring is done during production for microbes and other contaminants. Please indicate how often sampling is performed for particulates and microbiological monitoring. For microbiological monitoring, how are microbiological samples collected, how are they cultivated and counted, and what acceptance criteria are used?

3. We refer to page 970113 (a report from , showing Microbial Limits results for 4 samples of talc from . The total bacterial count (TBC) ranged from TBC per gm to TBC per gm. These results are in contrast to the statement by on page 970222, which suggests the Microbial Limits Test is not needed, and the samples will be tested by a sterility test because they are expected to be sterile. It appears there is confusion over the sample being tested.

   a. Are these samples of packaged product which are being tested PRIOR to sterilization, or are these samples of bulk drug substance, i.e. talc? If supporting data are available, summaries would be helpful.

   b. If there are Microbial Limits acceptance criteria for the drug substance, they should be stated.

   c. If the sterility test is used, will sterility test acceptance criteria be employed and the lot rejected if found to be non-sterile?

4. We refer to the Sterility Test method provided on page 970223.

   a. The test method does not state how many canisters of Sclerosol are tested for sterility or how the samples are selected.

   b. The test method does not state how the drug is transferred from the container into the growth media.

5. We recommend that this product be tested for endotoxins prior to its release and a limit should be provided to the NDA. Due to the nature of the product, there is no need for endotoxins testing to be part of the stability program. You may wish to refer to the Agency's "Guideline on validation of the Limulus amebocyte lysate test as an end-product endotoxin test for human and animal parenteral drugs, biological products, and medical devices " (1987).

Please note that any deficiencies in the referenced Drug Master File (DMF) will be conveyed to the DMF holder separately.

During recent inspections of the manufacturing facilities for your NDA, a number of deficiencies were noted and conveyed to you or your suppliers by the inspector. Satisfactory inspections will be required before this application may be approved.

In addition, it will be necessary for you to submit revised draft labeling identical in content to the attached draft labeling. Please note that we may have additional revisions to this labeling once we have completed our review of your response to this letter.

If additional information relating to the safety or effectiveness of this drug becomes available, further revision of that labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting any new safety information you have received since submitting your NDA. This should include all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications, HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

Under 21 CFR 314.102(d) of the new drug regulations, you may request an informal meeting or telephone conference with the Division to discuss what further steps need to be taken before the application may be approved.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

If you have any questions, please contact Debra Catterson, Project Manager, at (301) 827-1544.

Sincerely yours,

/S/

10/27/97

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

cc:

Original NDA 20-587
HFD-150/Div. Files
HFD-002/ORM
HFD-92/DDM-DIAB
HFD-80
HFD-150/DCatterson
HFD-150/AMartin
HFD-150/JBeitz
HFD-150/RBarron
HFD-150/RWood
HFD-150/WSchmidt
HFD-150/PAndrews
HFD-150/ARahman
HFD-150/LKieffer
HFD-150/CGnecco
HFD-805/DHussong
HFD-350/NSager
HFD-101/Office Director
DISTRICT OFFICE
HFD-40/DDMAC (with draft labeling)
HFD-560/OTC (with labeling - for OTC Drug Products Only)
HFD-150/DWPease

Drafted by: DCatterson/October 22, 1997/c:\wpfiles\nda's\talc\letter.ae2
r/d initialed by:
DPease/ 10-23-97
AMartin/10-24-97
JBeitz/10-24-97
RBarron/10-24-97
RWood/10-27-97 (with revisions)
WSchmidt/10-23-97
PAndrews/10-24-97
ARahman/10-23-97
LKieffer/10-23-97

10-27-97

F/T by DPease/10-27-97
DPease/
RDeLap/ 10/27/97

APPROVABLE (AE)

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-587

AUG 9 1996

Bryan Corporation
4 Plympton Street
Woburn, MA 01801

Attention: Frank Abrano
Chief Executive Officer

Dear Mr. Abrano:

Please refer to your August 11, 1995 new drug application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Sclerosol Intrapleural Aerosol (sterile talc powder).

We acknowledge receipt of your amendment dated January 24, 1996.

We have completed the review of this application as submitted with draft labeling, and it is approvable. Please note that the tradename has been changed to **Sclerosol Intrapleural Aerosol**, and the established name has been changed to **sterile talc powder**. Before this application may be approved, however, it will be necessary for you to respond to the following deficiencies.

The following deficiencies pertain to the chemistry portion of your application:

1. Every lot of bulk talc used in the manufacture of the sterile aerosol talc must be certified as asbestos-free. All specifications for the testing for the absence of asbestos, such as the "Sales Specification Sheet" on p. 2-009 of the submission provided by should be revised and provided.

2. Complete information, including the source, specifications, lot number, storage, container/closure, handling, etc., should be provided on reference standards.

3. the supplier of the bulk talc, should provide a complete description of the container-closure and container labeling used for storage and shipment of the bulk material.

4. With regard to the particle size measurement on the bulk talc by please address the following concerns:

a. The particles retained by the sieve should be characterized by microscopic inspection, such as, morphology, single particles or agglomerates. Is there any evidence of aggregation or agglomeration?

b. The potential problem of electrostatic charge build-up on the material particles is not discussed. Is this a problem, and if so, how is it addressed?

c. The method does not provide information on "fines," or particles of extremely small diameter, in the sample. A second test procedure for the lower end of the particle size range may be required, if such a sieve is available. Otherwise an independent method should be used to provide these data.

d. Detailed information on the type of sieve used with the method should be provided (electroformed or perforated plate, for example), as well as sieve series, (ASTM, Tyler, BSS, ISO, R-565, USP, other), material of construction, sieve diameter, etc.

5. With regard to the particle size distribution by the method, please provide the following information:

a. The procedures, including the reference standards over the entire range of particle sizes, used to calibrate the instrumentation and the expected accuracy of the measurements should be provided. Validation and system suitability tests for the technique should be provided to demonstrate that the method is capable of sufficient sensitivity and discriminatory capability to determine any lot to lot variations of the product.

b. Specifications and limits should be established which would be applicable to the distribution curve data to control the particle size of the talc. A numerical means, such as the distribution limits at 90%, 50% and 10%, based on actual results, should be added to adequately characterize the material.

6. A particle size measurement using USP 23 methodology under USP General Chapter 601 > Aerosols should be added to the release specifications of the finished product. Adequate justification, including validation data, should be provided for the method selected.

7. The submitted documents for thermogravimetric analyses (TGA) are for analyses of Grade 0X0 Data on Grade 00 talc by method MC 8 should be provided. Additionally, the basis for the theoretical weight loss for the product

used in the calculations of chlorite, dolomite and talc content should be provided, since the molecular stoichiometry of the chlorites is complex. Please also address the following:

a. The description of the method should indicate if the samples undergo prior treatment, such as additional drying prior to TGA.

b. Based on literature reports, TGA can be used to quantify the percentage of impurities in talc samples. Please indicate if the presence of calcite, carbonate (as loss of CO_2), or organic material has been observed by TGA.

8. The test results for CFC 12 (Algofrene 12), provided as Exhibit 8 of the Establishment Inspection Report of SMA, are not considered specifications. Please submit specifications, including limits, and test methods, for the product, Algofrene 12.

9. With regard to the manufacturing and in-process controls for the finished product, please address the following:

a. Confirm the observation in the Establishment Inspection report that the pressure test for the product is the USP 23 methodology under General Chapter <601> Aerosols for continuous release valves. Revise the narrative to reflect this information.

b. Provide a complete description, including source, diameter, porosity, etc., of the in-line filter on the CFC filling line used in the manufacture of the aerosol product.

c. Provide complete information on the operation for the crimping of the valve to the canister body, including all controls and measurements, such as crimp force and inspections, used to ensure a leak-proof seal.

d. Provide the information encoded on the canister bottom by ink-jet printing. This information should include the propellant type, expiration date, etc.

e. Provide information on the moisture content of the finished product.

f. Provide the information on the testing protocol used to determine leakage and canister resistance to excess pressure, including the following:

i. Limits on the temperature of the bath.

ii. A detailed description of the leakage testing including number of cans tested from each lot (sampling plan), method used to submerge canisters, position during submersion, etc., should be provided.

g. Provide the temperature limits and controls on the hot air blower used to dry the product after submersion testing.

h. Provide the sampling plan and details involved in the drainage testing for the product.

i. Provide a description of the shipping carton for the product for shipment to the secondary packaging firm.

j. Provide the disposition of product which fails the in-process or release testing criteria. Is any part of the product salvaged or reworked?

10. The methodology used to pressure test the product at release should be provided. We recommend the method in USP 23 General Chapter <601> Aerosols for continuous release valves.

11. Concerning the container/closure for the product:

a. Dimensional drawings of all container/closure components should be provided.

b. A full description, including composition, average thickness, application method, drying method and time etc. of the X-ray resistant coating , of the canister interior is requested. Results of tests to demonstrate compatibility with the product and propellant and the nature and levels of any extractables found from this coating, using compendial methods, should be provided. To maintain confidentiality, the composition information, which should include the exact citation to 21 CFR 175.300, may be contained in a Drug Master File as described in the FDA Guideline for Drug Master Files, September 1989.

c. A full description of the catheter should be provided. This should include source, dimensional drawings (particularly inside and outside diameters), composition (indicating any plasticizers), data on extractables, and the results of compatibility studies with propellant/product.

d. A full description of the components of the canister valve, including composition, is required. Studies to determine the nature and levels of any extractables from the components, such as gaskets, should be performed.

e. The composition and supplier of the actuator (button) should be provided.

f. Complete information on the canister labeling and the accompanying package insert should be provided. The details of the overwrap should also be included.

g. Information on the canister dip tube, including composition, size, and means of attachment to the valve, should be provided in the submission.

h. Information on the cap or cover for the canister, such as source, composition, etc., should be provided.

12. A stability protocol, as described in the FDA Guideline, should be provided to monitor the following characteristics of the product: leakage (weight), drainage or empty weight, canister pressure, spray function including plume geometry, particle size, distribution, levels of any extractables, microbial quality and interior coating and valve condition at the end of proposed expiration date.

13. Concerning the canister labeling, a mock-up or actual copy of the information which will appear on the sterile overwrap of the product should be provided. The method or means of application should also be provided.

14. The problem of detachment of the catheter tube during use of the product due to the pressure of the spray, should be addressed. It is our understanding that a modification of the actuator has been made which includes the permanent attachment of the catheter to the actuator. Please provide complete information on all modifications, such as source and type of adhesive, etc.

15. Reports of damage to the tissue of the lung and pleural cavity of patients due to the catheter tube of the product have been cited. Have any attempts been made to alleviate this problem by modification, such as rounding or flaring of the catheter tip? What options relative to the catheter and tip geometry have been investigated to prevent patient injury?

16. Observations of "clumping" of talc in the catheter tube have been reported. Please provide any information, such as moisture content, formulations, results of investigative studies etc., relative to this problem.

17. The following comments, relating to the sterilization and microbial testing aspects of the product, should also be addressed.

a. Please provide a brief summary of the product sterilization validation data. The

following supporting information would be helpful:

i. Was the sterilization dose kGy) developed on the basis of bioburden in the product prior to irradiation? If, so, what microbiological results were observed?

ii. Was dose mapping performed? If so, what were the minimum and maximum doses?

iii. Were biological indicators used to challenge the minimum sterilization process kGy) for the product?

b. We note the certificate on page 79 indicating a dose of kGy was delivered to the product batch numbers 88/06 - 89/06. Was this a minimum dose, maximum dose, or average dose? Why was this sub-process dose done?

c. We refer to the microbiological test methods provided on pages 2-111 through 2-135.

i. The methods do not address the collection of microbiological samples from a pressurized container. An example of suitable methods may be found in USP 23 <61>, page 1684, for samples in aerosol containers.

ii. The methods do not address sampling the spray actuators and catheters. A suitable method may be found in USP 23 <71>, pages 1689 (immersion) and 1690 (filtration).

iii. The microbial testing methods described were developed for products intended to be non-sterile. Since the product is labelled as sterile, a compendial sterility test may be simpler to perform. For example, the "SMA methods" described various tests using many different primary and secondary growth media. However, if any evidence of growth was observed in an enrichment culture, this would demonstrate a sterility failure and there would be no need for further selective cultivation for the purpose of demonstrating microbial contamination.

The following deficiencies pertain to the microbiology portion of your application:

1. Please specify the sterility test methods performed by with particular reference to sample collection to test the talc aerosol.

2. Please clarify the specifications pertaining to microbiology for the "bulk product" which is tested for sterility (item #4b of contained in the amendment). If this bulk is not specified to be sterile, it would be better to test this for Microbial Limits (USP) rather than Sterility. If the bulk is specified to be sterile, the sterilization process was not described in the August 11, 1995 submission. That submission indicates the talc is packaged and sterilized by a process.

3. Please specify the item "product" tested by the Microbial Limits Test (item #2 of contained in the amendment). An explanation of the items tested, the purpose of the test, and acceptance specifications should be provided. Does this test apply to finished product, or to components prior to irradiation?

The following deficiencies pertain to the environmental assessment (EA) portion of your application:

1. Information should be provided in the EA on the disposal method of rejected, returned, or expired goods. Will the CFC's be recovered? The identity and permitting information including permit expiration date, if any, should be provided for the currently used facilities.

2. The controls used to limit CFC emissions during manufacture of the finished product should be described as well as the disposition of waste CFC's.

In addition, it will be necessary for you to submit revised draft labeling identical in content to the attached draft labeling. Please note that we may have additional revisions to this labeling once we have completed our review of your response to this letter.

If additional information relating to the safety or effectiveness of this drug becomes available, further revision of that labeling may be required.

Under 21 CFR 314.50(d)(5)(vi)(*b*), we request that you update your NDA by submitting any new safety information you have received since submitting your NDA. This should include all deaths and any adverse events that led to discontinuation of the drug and any information suggesting a substantial difference in the rate of occurrence of common but less serious adverse events. The update should cover all studies and uses of the drug including: (1) those involving indications not being sought in the present submission, (2) other dosage forms, and (3) other dose levels, etc.

In addition, please submit three copies of the introductory promotional material that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final

print. Please submit one copy to this Division and two copies of both the promotional material and the package insert directly to:

Food and Drug Administration
Division of Drug Marketing, Advertising and Communications,
HFD-40
5600 Fishers Lane
Rockville, Maryland 20857

Within 10 days after the date of this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.110. In the absence of such action FDA may take action to withdraw the application.

The drug may not be legally marketed until you have been notified in writing that the application is approved.

Should you have any questions, please contact:

Debra Catterson
Project Manager
Telephone: (301) 827-1544

Sincerely yours,

/S/ 3/9/96

Robert Temple, M.D.
Director
Office of Drug Evaluation I
Center for Drug Evaluation and Research

ENCLOSURE

cc:
Original NDA 20-587
HFD-150/Div. Files
HFD-2/M.Lumpkin
HFD-80
HFD-150/CSO/DCatterson
HFD-150/AMartin
HFD-150/LKieffer
HFD-150/RBarron
HFD-150/WSchmidt
HFD-150/ARahman
HFD-150/CGnecco
HFD-805/DHussong
HFD-350/NSager
HFD-101/L.Carter (with labeling)
DISTRICT OFFICE
HFR-MA100
HFD-40/DDMAC (with draft labeling)
HFD-560/D.Bowen (with labeling - for OTC Drug Products Only)

drafted: DCatterson/July 23, 1996/c:\wpfiles\nda's\talc\letter.ae
r/d Initials:
DPease/7.29.96
AMartin/8.6.96
LKieffer/8.6.96
RJustice/8.7.96
RBarron/8.5.96
RWood/8.7.96
WSchmidt/8.5.96
JDeGeorge/8.5.96
ARahman/8.6.96
CGnecco/8.3.96
CHoiberg/8.7.96
RDeLap/8.7.96

F/T by DCatterson/8.8.96
DPease/ for 8-8-96
RDeLap/RD 8-8-96

APPROVABLE (AE)